Early-onset twin–twin transfusion syndrome: Case series and systematic review

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Abstract

Introduction: Data on the outcomes of early-onset twin–twin transfusion syndrome (TTTS), diagnosed before 18 weeks gestational age (GA), are sparse. We aimed to review the diagnosis, management and outcomes of early-onset TTTS.

Material and methods: Pregnancy records at a single referral unit 2010-6 were reviewed. In early-onset TTTS cases, data for pregnancy characteristics, interventions and outcomes were collected. PubMed and Scopus databases were searched for studies including pregnant women with early-onset TTTS. The primary outcome measure was livebirths.

Results: Case series: 58 cases of early-onset TTTS 2010-6, with full outcome data in 44. Diagnostic criteria were variable. Median GA at intervention was 17^{+4} (range 15^{+0}-28^{+1}); 67% of patients had laser therapy (39/58). Overall survival: 60% (53/88). At least one livebirth: 86% (38/44), Two livebirths: 34% (15/44); No survivors: 14% (6/44). GA at delivery was $32^{+1.5}$ (range 16^{+2}-37^{+4}). Systematic review: 16 studies included (n = 171 pregnancies). Diagnostic criteria varied widely: 79% of studies used Quintero staging. Most offered laser (89%) at median 17^{+0} weeks (range 16^{+0}-21^{+6}). GA at delivery was 23^{+0}-39^{+5} weeks. Overall survival: 69% (129/186). At least one livebirth: 74% (127/171). Two livebirths: 59% (55/93). No survivors: 26% (44/171).

Conclusions: In comparison with the commonly accepted overall survival for TTTS treated after 18 weeks of 60–90%, outcomes in early-onset TTTS were at the lower bound of this range. Gestational age at intervention is similar to that of later onset TTTS, indicating a lack of therapeutic options when a diagnosis is made before 18 weeks.

Keywords: multiple pregnancy, twin–twin transfusion syndrome, fetal therapies, pregnancy outcome, diagnostic imaging criteria.

Introduction

Twin–twin transfusion syndrome (TTTS) is a complication of monochorionic diamniotic (MCDA) twins and accounts for the majority of their morbidity and mortality.[1] TTTS affects 8–15% MCDA pregnancies, with 7–23% of cases requiring treatment prior to 18 weeks' gestation in large prospective studies ('early-onset' TTTS).[2–5]

The severity of TTTS is categorised typically using Quintero Stages I–V, based on standardised ultrasound findings.[6] This staging system was validated for diagnosis of TTTS from 18 weeks' gestational age (GA) onwards but is not prognostic.[7,8] In the two decades since the Quintero system was developed, a number of other indicators have been studied, including nuchal translucency, abnormal ductus venosus flow velocity waveform, abdominal circumference (AC) ratio and crown-rump length discrepancy.[9,10] Adjustment related to gestational age of values for deepest vertical pool (DVP) has also been considered and used in research studies for later gestations.[11] Despite this, there are currently no validated criteria to accurately diagnose early-onset TTTS.

Treatment of TTTS includes conservative management, fetoscopic laser photocoagulation, amnioreduction, septostomy, selective reduction by radiofrequency ablation (RFA) or cord occlusion, or termination of pregnancy.[12] Even after laser ablation, the mortality is up to 30–50%, and 5–20% babies may develop neurological sequelae.[1,13]

TTTS diagnosed before 18 weeks' GA is common[4,5]; however, specific data on the characteristics and outcomes of this subset of cases are sparse. TTTS at extremely early gestations

poses difficulties in diagnosis and categorisation, with many cases seen at the start of the second trimester not conforming to commonly used criteria, particularly in relation to amniotic fluid discrepancy.[14] Management can be challenging, as access to the intrauterine space may be delayed, awaiting chorio-amniotic fusion beyond 16 weeks' gestation.[15] For these reasons, early-onset TTTS may be under diagnosed or under reported in the literature. With advances in ultrasound technology and its applications, the diagnosis, natural history and management of TTTS at earlier gestations merits further understanding.

The aims of this paper are to describe the characteristics and outcomes of early-onset TTTS cases treated at our unit and to systematically review published literature regarding the characteristics and outcomes of pregnancies affected with early-onset TTTS.

Material and methods

Case series

Retrospective analysis of routinely collected pregnancy data was performed as part of ongoing internal audit processes within organization. Collection of the data for the purposes of audit was approved by Imperial College NHS Hospital Trust; as no additional data was collected for this study, separate ethical committee approval was not required.

Our unit is a UK tertiary referral centre which accepts complicated monochorionic pregnancy cases from a group of hospitals for which the total annual delivery rate is 28,000. All cases of MCDA twin pregnancies January 2010–February 2016 were identified by searching our electronic database of ultrasound examinations. Included cases all had a diagnosis of TTTS (staged or unstaged) documented before 18 weeks GA, regardless of ongoing management. This included MCDA twins with 'pre-stage' TTTS (a clinical judgement based on the finding of a stuck twin (bladder present) without DVP > 8 cm in the recipient and normal fetal Dopplers). MCDA twins with a discrepancy of weight > 20% were included if TTTS coexisted. Cases were excluded if part of a higher order pregnancy, there was a known congenital fetal abnormality or abnormal karyotype, or chorionicity was assigned after 14 weeks' GA. Fetoscopic laser was carried out with the Dornier Medilas D MultiBeam (Dornier MedTech, Wessling, Germany) and 2mm 30-degree fetoscope (Karl Storz GmbH, Tuttlingen, Germany). RFA was performed with the RITA® System Generator 1500X (AngioDynamics, Latham, NY, USA) and the RITA StarBurst SDE Electrosurgical device (Angiodynamics).

The primary outcome was survival of one or both twins to delivery, defined as a live-born fetus delivered at or after 23^{+0} weeks' GA. Secondary outcomes were GA at delivery, birthweight, mode of delivery, ultrasound findings at diagnosis of TTTS, pregnancy characteristics at intervention for treatment of TTTS, intervention used, progression of TTTS, twin anaemia-polycythemia syndrome (TAPS), pre-term labour, pre-term rupture of membranes, maternal antepartum haemorrhage, and maternal or fetal iatrogenic injury. Data were collected from electronic patient record databases and patient paper-based notes where required for additional information.

Systematic review

A literature search was carried out from inception to April 2016 on PubMed searching Medline, EMBASE, The Cochrane Library and ClinicalTrials.gov. Reference lists of retrieved reports were also searched for any additional studies. The search included relevant medical subject heading (MeSH) terms, keywords and word variants for 'twin' 'monochorionic', 'diamniotic' and 'twin-twin', 'feto-fetal', 'transfusion syndrome', 'placental anastomoses', 'selective growth restriction' and 'twin reversed arterial perfusion'. No further qualifiers were used, so as to provide the broadest search possible and identify the maximum number of relevant studies. The search was limited to the English language and restricted to human studies. Studies were graded according to Level of Evidence hierarchy. Quality and bias of cohort studies was further assessed using the Newcastle–Ottawa quality assessment scale, giving a score out of 9 for each study (Table 1). Data were extracted on the quality and characteristics of the studies and outcomes as listed above. Outcomes were based on combined data from all studies and calculated as percentages of all cases. Due to the high heterogeneity of inclusion criteria and outcomes within the studies, metanalysis was deemed not to be appropriate. PRISMA guidelines were adhered to.

All study types containing primary data were considered for inclusion; RCTs, cohort, case control, case series and case reports. Participants were women with MCDA twins with an antenatal diagnosis of TTTS at < 18 weeks' GA. Studies including pregnancies affected by both TTTS and fetal growth restriction (FGR, as defined by the publishing authors) were also included, and presence of FGR was noted. Studies including pregnancies at >18 and <18 weeks' GA were included if data were available separately for the early-onset group, either in publication or by contacting the authors.

Exclusion criteria included studies reporting only cases of higher order pregnancies abnormal karyotype, congenital fetal anomalies. All studies were assessed for inclusion independently by two reviewers (NH and CJS), and data were subsequently extracted for analysis and double checked for accuracy (NH, CJS and BML). Any disagreements were resolved through consulting another author.

The primary outcome measure was livebirths. Secondary outcome measures assessed pregnancy- and procedure-related outcomes. Pregnancy-related outcomes included birthweight, GA at delivery, mode of delivery, neonatal morbidity and survival of twins to 6 months of age. Procedure-related outcomes included pregnancy loss, pre-mature/spontaneous rupture of membranes and pre-term birth within a specific time frame

Table 1: Newcastle–Ottawa quality assessment scale for cohort studies included in systematic review.

Study	Selection				Compa-rability	Outcome			Total	Quality
	S1	S2	S3	S4	C1	O1	O2	O3		
Lecointre et al. (2014)[5]	*	*	*	*	*	*	*		7	Good
Sepulveda et al. (2007)[32]	*		*	*	**	*	*	*	8	Good
Fichera (2010)	*		*	*	**	*	*	*	8	Good
Fichera et al. (2015)[21]	*		*	*	*	*	*	*	7	Good
Ortiz et al. (2016)[22]	*	*	*	*	*	*	*		7	Good
Persico et al. (2016)[23]	*		*	*	*	*	*		6	Good

Selection: S1 Representativeness of the exposed cohort, S2 Selection of the non-exposed cohort, S3 Ascertainment of exposure, S4 Outcome of interest not present at start of study. Comparability: C1 Comparability of cohorts on the basis of the design or analysis controlled for confounders. Outcome: O1 Assessment of outcome, O2 Adequacy of duration of follow-up, O3 Adequacy of completeness of follow-up.
THRESHOLDS: Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

after the procedure as defined by authors. Any post-procedural changes in TTTS status, additional procedures carried out as well as any iatrogenic or maternal complications were also recorded.

Statistical analysis

All statistical analysis was performed in SPSS (version 22, IBM, NY, USA). Graphs were drawn in GraphPad Prism (version 6, GraphPad Software, Inc., San Diego, CA, USA). Statistical significance was accepted when $P < 0.05$ for all tests, although where applicable individual P values are presented in text, graphs and tables.

Continuous data were assessed for normality using the Shapiro–Wilkes test. Descriptive analysis was performed using mean $\pm$ standard deviation (SD) was used for normally distributed data. Median and range or 95% confidence intervals were used for non-parametric continuous data.

Proportions of categorical data are described as percentage with a 95% confidence interval given. A chi-squared test was used for univariate analysis of categorical data where indicated.

Ethics approval

The study did not require research ethics approval and the data was collected as a registered Trust audit.

Results

Case series

There were 867 MCDA pregnancies assessed in our unit 2010–2016; 58 were diagnosed with early-onset TTTS. Median GA at diagnosis was 16^{+5} (range 15^{+0}–17^{+6}) GA. Birth outcome data were available for 44 of these pregnancies (76%). Maternal demographics are given in Table 2.

TTTS Stage III was the most common stage at diagnosis 23/58 (40%). Quintero staging was applied to 48/58 (83%) of TTTS diagnoses before 18 weeks gestation; 10 cases which were classified as TTTS had amniotic fluid discrepancy insufficient to meet the criteria for Stage I. The mean absolute difference in DVP between recipient (R) and donor (D) was 5.9cm (SD $\pm$ 1.9cm), similar to the mean DVP ratio (R/D) of 5.8 (SD $\pm$ 5.6) (Table 2).

The majority (39/58, 67%) of cases were managed using fetoscopic laser photocoagulation, median GA at laser was 17^{+4} (range 16^{+0}–28^{+1}). Radiofrequency ablation was the next most used management strategy (12/58, 21%), median GA at intervention was 17^{+3} (range 15^{+0}–22^{+1}); 8/12 (67%) pregnancies had coexisting discrepancy in fetal weight >20%; and 6/12 (50%) had Stage III-IV TTTS. None of the 6/58 (10%) pregnancies opting for conservative management had Stage III-IV TTTS. The remaining 2% opted for termination of pregnancy. There were no cases of amnioreduction. The median time from diagnosis TTTS (all stages) to invasive treatment was 2 days (range 0–87); for pregnancies Stage II–IV at diagnosis, the median time to invasive treatment was 0 days (range 0–16).

Pregnancy outcomes are given in Table 3. Overall survival was 60% (53 of 88 potential surviving fetuses); 86% (38/44) of pregnancies had at least one livebirth; 34% (15/44) of pregnancies had two livebirths, and in 14% (6/44), there were no livebirths (Figure 2). Median GA at delivery if born alive was 33^{+2} (range 23^{+6}–37^{+4}); the rate of pre-term delivery at <32 and <28 weeks' GA was 42% and 21%, respectively. Mean birthweight (born alive, recipient) was 1910 g (SD $\pm$ 522 g) and (born alive, donor) was 1439 g (SD $\pm$ 535 g). Pregnancies with Stage $\geq$ III TTTS at diagnosis had an overall survival of 44% (16/36 potential surviving fetuses); 72% of pregnancies had at

Table 2: Maternal demographics and characteristics at diagnosis for case series of early-onset TTTS.

Maternal demographics	
Number of cases	58
Maternal age (years)	27.5 (15–42)
Nulliparous	18/29 (62%)
BMI (kg cm^{-2})	26.7 ± 1.9
IVF	4/18 (22%)

Characteristics at diagnosis	
Number of cases	58
Gestational age	16 + 5 (15 + 0–17 + 6)
'Pre-TTTS'/unstaged TTTS	17% (10–29%)
TTTS stage I	19% (11–31%)
TTTS stage II	24% (15–37%)
TTTS stage III	40% (28–53%)
TTTS stage IV	0% (0–1%)
TTTS stage V	0% (0–1%)
Weight discordance > 20%	31% (21–44%)
Absolute DVP Difference (cm)	5.9 ± 1.9
DVP ratio (R/D)	5.8 ± 5.6

Table 3: Outcomes for case series of early-onset TTTS.

Outcomes at delivery	
Number of cases	44
At least 1 livebirth	86% (73–94%)
2 Livebirths	34% (22–49%)
No livebirth	14% (6–27%)
Gestational age	32 + 1.5 (16 + 2–37 + 4)
Gestational age (if alive)	33 + 2 (23 + 6–37 + 4)
Recipient birthweight (g)	1912 ± 507
Donor birthweight (g)	1401 ± 534
Recipient birthweight (g) if alive	1910 ± 522
Donor birthweight (g) if alive	1439 ± 535
Caesarean	15/23 (65%)
Vaginal delivery	8/23 (35%)

Prenatal outcomes	
Number of cases	58
Progression or stable (stage ≥ II) of TTTS	47% (32–63%)
Improvement or stable (stage I) of TTTS	53% (37–68%)
Pre-term delivery < 37/40	88% (69–96%)
Pre-term delivery < 32/40	42% (25–62%)
Pre-term delivery < 28/40	21% (9–40%)
Miscarriage	8% (2–26%)
Twin anaemia-polycythemia syndrome	0% (0–1%)
PROM < 32/40	8% (2–26%)
PROM < 28 days from procedure	2% (1–9%)
Maternal bleeding	4% (1–12%)
Maternal iatrogenic injury	0% (0–1%)
Fetal iatrogenic injury	0% (0–1%)

least one livebirth (13/18); the median GA at delivery was 34^{+0} (range 16^{+2}–37^{+4}).

In pregnancies treated by fetoscopic laser photocoagulation, the overall survival was 66% (38 of 58 potential surviving fetuses); 86% had at least one livebirth (25/29); 45% (13/29) had two livebirths, and in 14% (4/29) there were no livebirths. Following treatment, TTTS stage deteriorated in 37%. In pregnancies treated with RFA, 92% (11/12) had a livebirth. This is not significantly different to the overall survival rate following laser (P = 0.62). In the 6 pregnancies opting for conservative management (all with stage I–II TTTS), all experienced spontaneous regression or had stable stage I TTTS. Four were discharged to their local units after 28 weeks' gestation and lost to follow-up; the remaining 2 pregnancies both had two livebirths. There were no pregnancies affected with stage III TTTS who declined invasive treatment against which to compare the fetoscopic laser and RFA subgroups.

Systematic review

A total of 16 studies were included in the systematic review; a schema detailing study selection is shown in Figure 1. The included papers consisted of seven case reports, six cohort studies and three case series published 1996–2016. They report diagnosis, intervention and outcome data in 171 MCDA pregnancies (n = 342 fetuses) complicated by early-onset TTTS.

Eleven studies used Quintero staging as diagnostic criteria for TTTS. There were no gestational-age related adjustments described to identify early-onset TTTS. Two papers were published before Quintero staging was described.[16,17] The remaining three studies each have differing methods of diagnosing TTTS. Guenot et al.[18] used MCA-PSV Doppler to identify fetal

anaemia at 17 weeks gestation. Su *et al.*[19] describe ultrasound findings at 14 weeks GA of cardiomegaly and generalised oedema in one twin with the other twin being relatively smaller. Finally Yamashita *et al.*[20] describe polyhydramnios in twin A with oligohydramnios in twin B however give a provisional diagnosis of TTTS as chorionicity has not been diagnosed.

The majority (89%) of pregnancies were managed using fetoscopic laser photocoagulation; the median gestational age at intervention was 17^{+0} (range 16^{+0}–21^{+6}). Selective reduction was used in 6%, termination of pregnancy in 2%, amnio-drainage in 2% and expectant management in 1% of cases. A single pregnancy was managed using intraperitoneal intrauterine transfusion at 14^{+0}.

Gestational age at delivery ranged from 23^{+0} to 39^{+5} with half of the papers included quoting an average GA at delivery between 30 and 34 weeks. There was at least one twin livebirth in 74% pregnancies (127/171); 59% (55/93, data on this not available from Ortiz *et al.*) had two livebirths; 26% (44/171) pregnancies had no livebirths. Outcomes from Ortiz *et al.* were not included in overall survival calculations, as they were divided only into pregnancies with no survivors and those with at least one survivor. There were 93 pregnancies with complete outcome data, and 129 individuals survived to birth, giving an overall survival of 69% (129/186) based on available data (Figure 2).

A number of other outcomes were reported within the cohort studies. Fichera *et al.*[21] reported four miscarriages, six cases of pre-term birth, 7 NICU admissions and one neonatal death in their ten cases of TTTS diagnosed before 18 weeks gestation. Ortiz *et al.*[22] report a miscarriage rate of 17% (13/78), 48% rate of pre-term delivery (31/78) and 39% rate of PPROM <32 weeks (25/78) in their patients who underwent fetoscopy

<18 weeks gestation. Rates of all these complications were lower in the patients who underwent fetoscopy >18 weeks. They also reported a 37% rate (29/78) of chorio-amniotic membrane separation in the early-onset patients which was higher than that of 17% (32/192) in those who underwent fetoscopy >18 weeks gestation. Persico *et al.* reported one case of PPROM <24 weeks leading to miscarriage and one neonatal death in the 29 patients who were diagnosed with TTTS before 18 weeks gestation.[23]

Other outcomes which were reported in case reports included intra-twin arteriovenous fistula of the placenta,[24] a pseudoamniotic band syndrome,[25] acute reversal of oligohydramnios–polyhydramnios sequence[16] and the difficulty in managing presumed TTTS in a twin pregnancy presenting with lambda sign.[20]

Outcomes which were reported in the case series' included three cases of intestinal complications following laser treatment of TTTS, two of which were diagnosed with TTTS before 18 weeks (one intestinal atresia and one necrotising enterocolitis),[26] and another paper looking at the incidence of pseudoamniotic band syndrome following laser to treat TTTS in which two of the eight cases were diagnosed and had surgery before 18 weeks gestation.[27]

Comparison of survival between case series and systematic review

The overall survival of 60% and 69% for case series and systematic review, respectively, was similar (ns, P = 0.14, Figure 2). The rate of two survivors at delivery was significantly higher in the systematic review than in our case series: 59% versus 34% (P = 0.006); the rate of no livebirths was not different: 19% versus 14% (P = 0.09). Expressed another way, the rate of one or
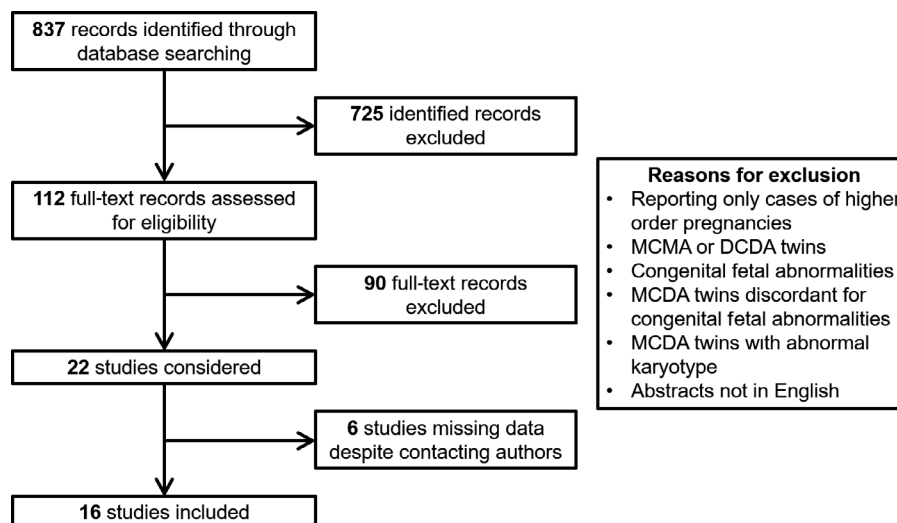
Figure 1: Studies Included in Systematic Review. Schema Detailing the Identification and Inclusion Process for Studies in the Review.
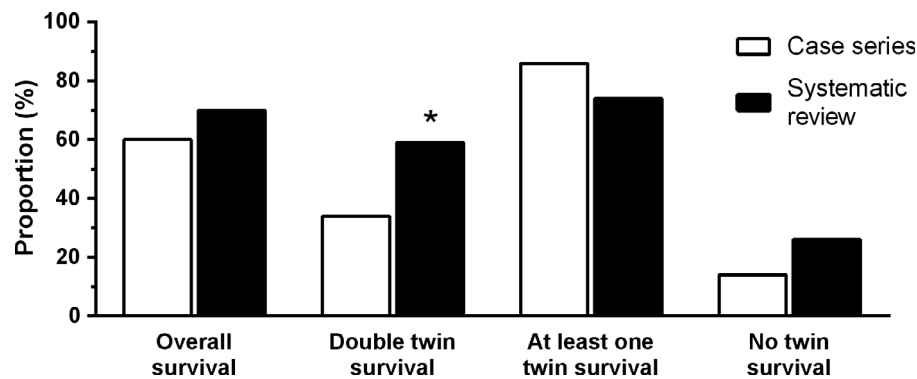
Figure 2: Comparison of Survival in Early-Onset TTTS. The Graph Shows the Proportions of Overall Survival, Double Twin Survival, Survival of at Least One Twin, and No Twin Survival Following a Diagnosis of Early-Onset TTTS Compared Between Our Case Series and The Data Derived from the Systematic Review. Proportions were Compared Using a Chi-Squared Test and * Denotes P < 0.05.

more twins born alive was not different between the case series and the systematic review: 86% versus 76 % (P = 0.09).

Discussion

Early-onset TTTS in this case series was associated with mortality at the higher margins of what might be expected for later onset TTTS, with just under two-thirds of all potential live-born fetuses surviving and half of patients showing improvement in TTTS. Of cases treated with laser; two-thirds of fetuses survived. Outcomes were worse for more advanced stages with fewer than half of cases diagnosed with Stage III TTTS surviving. The rate of pre-term birth before 32 weeks (42%) and a 65% Caesarean section rate highlights the maternal and fetal morbidity associated with early TTTS. Therefore, while early-onset TTTS, diagnosed using Quintero staging, makes up less than a quarter of the cases of TTTS seen, it contributes to a significant proportion of pregnancy loss.[2,5,28,29]

However, this may still represent an underestimation of the true rate of early-onset TTTS, as cases of liquor discrepancy leading to intrauterine fetal death may not be classified as TTTS. In a prospective cohort study of 200 MCDA twins,[14] there were eight double intrauterine fetal deaths, three of which were attributed to TTTS. Yet a further 3 of 8 double intrauterine deaths occurred between 13 and 16 weeks' gestation with 'severe amniotic fluid discrepancy', with oligohydramnios in one twin, and DVPs of 6.1–7.3 cm in the other, indicating the likely cause of fetal demise as TTTS. The earliest that TTTS was diagnosed using Quintero staging in both the case series and the systematic review was 15 weeks' gestation. However, evidence of amniotic fluid discordance not meeting the criteria for Stage I may have been evident earlier than recorded here, with signs likely detected in local hospitals before referral. In up to 17% of cases, the diagnosis was evident without formal staging based for

example on the Quintero criteria: in all cases, there were additional feature of TTTS, with oligohydramnios in the donor, but a DVP < 8 cm in the recipient. Similarly, in the 14 post-Quintero studies in the systematic review, modified criteria were used in 3. This variance in practice could be due to the lack of specific diagnostic criteria for early-onset TTTS. Just as an increase in the DVP threshold to diagnose polyhydramnios has been proposed at gestations over 20 weeks to account for changes in the size of the uterus and fetal urinary production,[11] a lower DVP threshold could be considered below 18 weeks' gestation. Fetal kidneys are functional from the late first trimester,[30] but before keratinisation of the fetal skin is complete at approximately 22–25 weeks of gestation, amniotic fluid volume is proportional to fetal size.[31] Therefore, at below 18 weeks' gestation, a DVP of over 6cm, in the presence of oligohydramnios in the other twin, could be considered polyhydramnios, and indicative of early-onset TTTS.

Lag times between diagnosis and treatment were seen of up to 87 days and, although these were shorter for more advanced stages of TTTS (≥Stage II), this has the potential for outcomes worsening before intervention takes place, as even in Stage I TTTS treatment results in better outcomes that expectant management.[27] There is likelihood that they experienced a lag in treatment due to technical difficulties, early gestation and fusion of the membranes.

The systematic review revealed a scarcity of studies on TTTS before 18 weeks, and only one paper specifically addressing early-onset TTTS. Some papers excluded miscarriage[22] some focused on particular outcomes at birth[25–27] and others looked only at cases treated with laser.[5,32] The earliest GA where laser was performed was 16 + 0 weeks for both case series and systematic review. Diagnostic criteria were largely based on the classification of Quintero and although there was discussion in some papers about alteration of this criteria after 20 weeks'

gestation, none of the literature addressed the lack of validated criteria <18 weeks.

Results from the case series were comparable to those from the systematic review, except for the rates of two twin survival, which was higher in the systematic review, but there was no difference in the rates of one or more twin or overall survival. This may reflect the difference between data which is published in a research environment and internal audit of outcome data from broader clinical practice. Our case series pregnancies treated with laser, selective fetocide, termination of pregnancy, conservative management, or that miscarried were all included in overall outcomes. Comparatively, taking into consideration publication and outcome reporting bias and the exclusion of miscarriages in some papers, the systematic review findings were more likely to overestimate rather than underestimate the true livebirth rate. Regardless, any of these figures demonstrate a real opportunity for improvement in survival outcomes for pregnancy complicated by TTTS. There is insufficient data to comment on rarer outcomes such as maternal morbidity and twin anaemia-polycythemia sequence (TAPS).

The strengths of this paper include that it is the first study to specifically address early-onset TTTS and includes a systematic review of other relevant studies. Data were not limited to a single treatment type but rather includes all cases of early-onset TTTS and how they were managed. The systematic review includes both published and unpublished data provided by authors, allowing for a comparative assessment among studies, and gives an insight into best available evidence on this topic.

The limitations are that the case series included relatively small numbers, although larger than any series previously reported. As we report on a largely a referred population, following treatment many of these patients returned to their referring hospitals for delivery, and despite efforts to follow these patients up outcomes remained incomplete for 24% of eligible patients. There is potential for us to have overestimated or underestimated livebirths: if all cases where birth data are missing had no livebirths, then overall survival would be 46%, if they were all livebirths, then overall survival would be 70%. Another drawback is missing outcome data and incomplete definitions of criteria used for diagnosis of FGR in the systematic review, although multiple efforts were also made to retrieve unpublished data from other authors.

Case reports in the literature show us that there are times when advanced stages of TTTS are diagnosed at very early gestational age, where cardiac function is compromised, at times with presence of hydrops. These cases do not however always meet the diagnostic criteria of amniotic fluid discrepancy or Quintero staging intended for >18 weeks. The challenge is how to make the diagnosis of early-onset TTTS before significant cardiac dysfunction occurs, to give a window of opportunity for intervention to improve outcomes. There is therefore a need to redefine the absolute thresholds for DVP or to develop other criteria for these early gestations.

Overall survival rates for TTTS which take into account all stages and management options are difficult to find, as the majority of studies focus on particular interventions or stage, and hence vary greatly: 63% from a multicentre study looking at TTTS outcomes in the 1990s,[33] 67% from a cohort of 18 patients,[34] 72% from 200 pregnancies with severe TTTS treated with laser,[35] and 90% from a cohort of 33 cases of TTTS.[21] The overall survival for early-onset TTTS from both our case series and systematic review (60% and 69%, respectively) are either similar to or slightly worse than aggregate survival rates of around 60–90% reported for TTTS at all gestations, as described above. Overall survival after treatment with laser has been reported as 75% with 85% of pregnancies resulting in at least one surviving fetus.[36] Comparatively our overall survival rate for twins with early-onset TTTS treated with laser was 66% (38/58) with 86% (25/29) having at least one surviving fetus.

Published outcomes for Stage III TTTS indicate an overall survival rate of 57% with at least one survivor in 74% of pregnancies.[37] Within our early-onset TTTS cases, initially diagnosed with Stage III, overall survival was 44% (16 of 36 potential surviving fetuses) with 72% of pregnancies with at least one survivor (13/18). What we can see from these comparisons is that overall survival appears lower in early-onset TTTS independent of treatment choice, or stage at diagnosis, compared to those diagnosed from 18 weeks onwards.

A prospective study would allow a more accurate comparison of treatment and outcomes for TTTS diagnosed <18 and >18 weeks gestation. There is also a need to investigate the potential for different and/or less invasive treatments which could be offered at earlier gestations, given the technical difficulty in instrumenting the uterus at early gestations, or at less severe stages of TTTS. Early treatment with fetoscopic laser ablation is thought to be associated with higher rates of pre-term rupture of membranes, chorio-amniotic separation with associated miscarriage[38,39] and pseudoamniotic band syndrome.[25,27] In their report of performing fetoscopic laser for TTTS below 17 weeks' gestation, Baud *et al.* report that the rate of pre-term rupture of membranes was inversely proportional to gestational age, with a 38% rate below 16 weeks, a 19% rate between 16 and 17 weeks and 6% after 17 weeks.[4] Conversely, Lecointre *et al.* report at 18% rate of pre-term rupture of membranes before and after 17 weeks' gestation. It is the concern regarding these complications that constrains when treatments can be offered to early-onset TTTS; this is reflected in the finding in both the studies by Baud *et al.* and Lecointre *et al.*, in which the stage of TTTS at treatment is significantly higher in the early-onset treatment group than the conventional treatment groups. Without the risks associated with invasion of the intrauterine space, such rationalisation of treatment for TTTS would not be necessary: it is possible that occlusion of anastomoses at earlier gestations and earlier stages of TTTS may be associated with improved outcomes.

Non-invasive treatments for TTTS are particularly suitable at earlier gestations prior to membrane fusion; our group has reported early stage proof of principle studies of high-intensity focused ultrasound (HIFU) selective occlusion of placental vessels in sheep, which appears to be both effective and safe, and first in human studies are planned.[40–43] In this proposed human treatment, thermal energy generated by externally placed, ultrasound guided, HIFU transducers will be used to selectively occlude placental anastomoses along the vascular equator of the monochorionic placenta, without the requirement to enter the intrauterine space. If non-invasive occlusion of placental anastomoses were possible, with an associated reduction in procedure-related risks, this would represent a paradigm shift in the gestations and severity at which TTTS could be treated.

Conclusion

Overall, our findings demonstrate that TTTS presenting before 18 weeks gestation in up to 25% of cases and carries a major risk of morbidity and mortality, with overall survival appearing to be less favourable than if diagnosed after 18 weeks, perhaps because invasive treatments are commonly deferred until after 17–18 weeks. The widely different criteria used in studies suggest there is a need to define a more rational basis for categorising early-onset TTTS and develop validated diagnostic criteria for use before 18 weeks of gestational age.

Funding

Conflict of interest

The authors declare no competing interests, financial or otherwise.

Authorship declaration

All authors are in agreement with the content of the submitted manuscript. The authorship listing conforms with the journal's authorship policy. Author contributions were as follows: CCL and CJS conceived and designed the study; BMF, NH, SL, CJS were involved in data collection; BMF and SM analysed the data for publication. BMF, NH, SL, CJS, SM and CCL drafted the article and revised it for important intellectual content.

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